REMARKS

Status of Claims and Amendment

Claims 1, 6-10, and 12-14 have been amended. Claim 2 has been canceled. Claims 1 and 3-14 are all the claims pending in the application. Claims 1 and 3-14 are rejected.

Claims 1, 6-10, and 12-14 have been amended to even further clarify the claimed invention, and to replace "host" with "patient" as suggested by the Examiner in response to a §112, second paragraph rejection.

In addition, claim 13 has been amended to recite "wherein the method prevents or treats graft verus host disease induced by donor lymphocyte infusion in the patient." Support for the amendment to claim 13 may be found at least at pages 16-18 of the specification.

Claim 14 has also been amended to further clarify that the composition containing whole bone marrow cells derived from the patient or derived from the third party with an identical HLA type as the patient is transplanted. Support for the amendment to claim 14 may be found at least at page 6, lines 18-23, page 7, lines 18-25, and page 18, lines 1-22 of the specification.

No new matter is added.

Response To Rejections Under 35 U.S.C. § 112

1. Indefiniteness Rejection

Claims 1 and 3-14 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite.

The Office Action asserts that claims 1 and 10 are unclear because the "host" recited in "HLA type as the host" lacks adequate antecedent basis. The Office Action suggests amending the claim to replace "host" with "patient" to overcome this rejection.

In response, and solely to advance prosecution of the present application, the claims have been amended as suggested by the Office Action, i.e., to replace "host" with "patient."

Reconsideration and withdrawal of the rejection under §112, second paragraph, is respectfully requested.

2. Enablement Rejection

Claims 12 and 14 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

The Office Action provides a detailed basis for this rejection at the bottom of page 3 to the top of page 4 of the Office Action.

The Office Action appears to assert that the specification teaches the individual use of the donor derived PBMC before the administration of either PBMC derived from the patient or derived from a HLA-identical individual, and whole bone marrow cells derived from the patient or derived from a HLA-identical individual. The Office Action also asserts that the specification teaches that PBMC derived from the patient or derived from a HLA-identical individual, is administered as a separate agent within 24 hours of administration of whole bone marrow cells derived from the patient or derived from a HLA-identical individual. Accordingly, the Office Action contends that the specification does not teach the combined use of PBMC derived from the patient or derived from a HLA-identical individual, and whole bone marrow cells derived from the patient or derived from a HLA-identical individual together.

Further, the Office Action contends that the specification provides no teachings regarding how to use a pharmacological composition including the donor derived PBMC as a third ingredient. The Office Action appears to assert that because of the lack of guidance in the

specification, one of ordinary skill in the art would require undue experimentation to make or use the claimed compositions.

In response, Applicants note that the specification provides ample guidance for one of ordinary skill in the art possessing common technical knowledge of the relevant art to make and use the presently claimed pharmacological composition for use in the treatment of a malignant tumor. One of ordinary skill in the art would understand from reading the specification, for instance, at page 9, line 9 to page 10, line 18, page 11, line 23 to page 16, Figs. 1 and 2, and page 14, line 17 to page 9, line 24, that the following compositions are administered in the following order for the claimed method of treatment.

First, donor lymphocyte infusion (DLI) is given to replace the hematopoietic system of the patient with that of the donor.

Second, the patient is subjected to irradiation treatment which eliminates the lymphocytes that cause GVHD (graft versus host disease).

Third, a HVGR (host versus graft reaction) is then induced by reconstructing the hematopoietic system of the patient, *i.e.*, replacing the donor-derived hematopoietic system with the hematopoietic system of the patient. The HLI is performed, for example, by intravenous administration (transfusion) of the host's peripheral blood mononuclear cells (PBMNCs)

Finally, the patient hematopoietic system is reconstructed by intra-bone marrow-bone marrow transplantation (IBM-BMT) which is performed with or after HLI to supplement the host's bone marrow with PBMNCs cells from a normal healthy person identical in HLA type so that the onset of GVHD is prevented, because the cells are able to secrete cytokines that inhibit the function of T cells.

In addition, and solely to advance prosecution of the present application, claims 12 and 14 have been amended to further clarify the order in which the claimed compositions are administered for the claimed method of treatment.

Reconsideration and withdrawal of the rejection under §112, first paragraph, is respectfully requested.

Response To Rejections Under 35 U.S.C. §103(a)

1. Matthes-Martin and Carella

Claim 10 is rejected under 35 U.S.C. §103(a) as being unpatentable over Matthes-Martin *et al.* (Bone Marrow Transplantation 26: 377-382 (2000); "Matthes-Martin") in view of Carella *et al.* (Bone Marrow Transplantation 25: 345-350 (2000); "Carella").

The Office Action asserts that Matthes-Martin teaches an allogenic stem cell transplantation method for treatment of juvenile myelomonocytic leukemia (abstract, first sentence). The Office Action states that Matthes-Martin teaches total body irradiation (TBI) as a method of pre-transplant conditioning and that TBI does not have a significant impact on treatment-related mortality. The Office Action points to the text immediately below Table 7 of Matthes-Martin for the teaching that "one patient received donor lymphocyte infusion followed by a 2nd bone marrow transplant." Accordingly, the Office Action states that Matthes-Martin teaches bone marrow as a source of stem cells for hematopoietic transplantation.

The Office Action asserts that Carella teaches stem cell transplantation by a donor lymphocyte infusion (DLI) containing mobilized blood stem cells (page 346, second column, lines 3-5 under the heading of "Focusing on immunosuppressive therapy pre-transplantation").

The Office Action states that it would have been *prima facie* obvious at the time the claimed invention was made to substitute a DLI comprising mobilized blood stem cells in place

of the bone marrow transplant used in the method of Matthes-Martin, including for treatment of the disclosed patient requiring a second transplant after DLI. The Examiner asserts that one of skill in the art would have been motivated to make the combination because Carella teaches the use of mobilized blood stem cells in a DLI and that it would be easier to obtain HLA-identical stem cells from mobilized blood stem cells from peripheral blood than from bone marrow which requires special procedures for removal from a donor. The Examiner also asserts that it would have been obvious to use total body irradiation (TBI) as a means of conditioning before the stem cell transplant because Matthes-Martin teaches that TBI does not have a significant impact on treatment-related mortality (TRM).

Initially, Applicants note that the Office Action has failed to establish a *prima facie* case of obviousness because Matthes-Martin and Carella, individually or in combination, do not teach or suggest each and every element of the claimed method. Pursuant to M.P.E.P. § 2143.03, to establish a *prima facie* case of obviousness, "all the claim limitations must be taught or suggested by the prior art."

Matthes-Martin is directed to the treatment of juvenile myelomonocytic leukaemia (JMML), and presents the data and disease course of eleven children who underwent BMT for JMML. (See page 377, 2nd column, lines 20-34 of column 2 of Matthes-Martin). Matthes-Martin discloses that eight of the eleven children received Ara-C and etoposide before BMT, while three of the children received mercaptopurine maintenance therapy only. (See page 378, column 1, lines 5-7 of Matthes-Martin). Matthes-Martin does not disclose the claimed method comprising performing DLI before irradiation treatment, followed by intravenous administration of peripheral blood stem cells for the following reasons.

First, although some of the patients were conditioned with TBI, it is unclear whether TBI is administered before or after BMT. For that matter, even if TBI is administered before the BMT, which does not appear to be the case based on the disclosure in Matthes-Martin, there still does not appear to be any teaching in Matthes-Martin that DLI is done before TBI. In fact, DLI is disclosed at page 379, column 2, 2nd full paragraph, to be only performed on patient UPN 293, who as shown in Table 2, did not receive TBI at all anytime during the course of treatment. It was not until after patient UPN 293 developed organomegally after BMT, had a splenectomy, and was placed on maintenance therapy with mercaptopurine, that DLI was performed. Also, Matthes-Martin teaches that even if DLI is performed, it is performed after BMT to "prevent and/or treat relapse after allogeneic BMT." (see page 382, 1st column, last sentence of 2nd full paragraph of Matthes-Martin).

In addition, Applicants note that Matthes-Martin neither teaches nor suggests the timing/order of performing DLI, TBI and BMT as presently claimed. Matthes-Martin only discloses that, even if DLI is performed, it is performed after BMT.

Matthes-Martin discloses the following procedures:

Procedure 1: TBI→BMT

Procedure 2: BMT→TBI*→BMT (*TBI is one year after BMT.)

Procedure 3: BMT→DLI→BMT

The above-mentioned Procedure 1 is derived from the description of UPN 109, 177, 186, 211, and 255 of Table 2 of Matthes-Martin. Procedure 2 is derived from the description on page 379, light column, lines 10-14 of Matthes-Martin, and relates to Patient UPN 255. Procedure 3 is derived from the description of Table 7, bottom and on page 382, left column, lines 20-22 of Matthes-Martin.

Second, based upon the teachings of Matthes-Martin, one of ordinary skill in the art would have been inclined to perform TBI after BMT. For instance, Matthes-Martin discloses that conditioning with TBI occurred one year after BMT and a second transplant for patient UPN 255. (See page 379, 2nd column, lines 10-13 of Matthes-Martin). In contrast, TBI is performed before BMT in the method of the present invention.

Third, as acknowledged by the Office Action, Matthes-Martin does not teach peripheral blood as a source of stem cells for hematopoietic transplantation. (See page 4, last sentence of 3rd full paragraph of Matthes-Martin). In this regard, Applicants note that the intravenous administration of peripheral blood as a source of stem cells (PBSCs) is performed in place of HLI and IBM-BMT. (See page 10, lines 19-24 of the present specification).

Further, even if the teachings of Matthes-Martin may be modified, one of ordinary skill in the art would not have had a reasonable expectation of success of obtaining the claimed method for the following reasons. First, Matthes-Martin discloses that although "BMT is the only curative approach for JMML…[it] is associated with a high TRM and a high relapse rate." (See page 379, 2nd column, 1st sentence under "Discussion", and see page 377, column 2, lines 19-22 of Matthes-Martin). Second, although Matthes-Martin teaches that TBI does not have a significant impact on transplant-related mortality (TRM), Matthes-Martin discloses that "TBI is associated with a significantly higher relapse rate." (See Abstract, lines 17-21 of Matthes-Martin). Specifically, Matthes-Martin found from a "[c]omparison of different conditioning regimens[,]...a significantly higher relapse rate in patients conditioned with TBI" (see page 381, 2nd column, 1st full paragraph of Matthes-Martin).

Thus, Matthes-Martin does not teach of suggest the steps of the claimed method.

Carella does not appear to cure the deficiencies of Matthes-Martin. Since it appears the Office Action is using Carella mainly for the teaching that stem cell transplantation by a donor lymphocyte infusion (DLI) may be from mobilized blood stem cells, Carella adds nothing further to the teachings of Matthes-Martin. In fact, one of ordinary skill in the art would not have had a reason or motivation to combine Carella with Matthes-Martin because Carella teaches away from the use of TBI. Carella discloses that because "results [support] the hypothesis that marrow grafts could create their own space and that myelosuppressive therapy was not necessary to establish allogeneic engraftment[,]…[t]hese observations, together with additional preclinical studies involving second T cell activation signal blockade, suggest that in the future TBI may be replaced with immunosuppressive agents that lack the desirable side-effects of ionizing radiation." (See page 347, 2nd column, last two sentences of 3rd full paragraph of Carella).

However, even if the teachings of Matthes-Martin and Carella are combined and the method of Matthes-Martin is modified to use mobilized blood stem cells for DLI, such a combination would not result in the claimed method because one of ordinary skill in the art would not have been guided to perform the steps of the claimed method based upon the teachings of Matthes-Martin for the reasons discussed above.

In this regard, Applicants note that even if, *arguendo*, DLI comprising mobilized blood stem cells described in Carella is applied to the procedure described in Matthes-Martin, instead of BMT in the procedure described in Matthes-Martin, the above-mentioned Procedures 1-3 are at best changed to the following procedures below.

Procedure 1': TBI→administration of mobilized blood stem cells

Procedure 2': administration of mobilized blood stem cells →TBI* →administration of mobilized blood stem cells

Procedure 3': administration of mobilized blood stem cells →DLI →administration of mobilized blood stem cells

In contrast, the presently claimed method performs DLI, irradiation treatment and PBSC, in this order. Thus, the presently claimed method is completely different from the above-mentioned Procedures 1'-3' that would be obtained from the combination of Carella with Matthes-Martin.

Accordingly, Matthes-Martin and Carella do not teach of suggest the presently claimed method of the present invention, and one of ordinary skill in the art would not have expected or predicted the treatment effects obtained by the presently claimed method. It would not have been obvious for one of ordinary skill in the art to obtain the claimed method from the combination of Matthes-Martin and Carella.

Reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.

2. Roush, Ballester, and Ikehara

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roush *et al.* (Transfusion Medicine Reviews 16: 161-176 (2002); "Roush"), the abstract of Ballester *et al.* (Blood 100(11): abstract no. 5198; "Ballester") and Ikehara et al (U.S. Patent No. 6,383,481; "Ikehara").

The Office Action states that "Roush teaches (DLI) therapy after stem cell transplantation." The Office Action asserts that Roush teaches that although disease remission has been attributed to DLI, the risk of graft vs. host disease may prevent the ultimate usefulness of DLI as a treatment.

Ballester is asserted by the Office Action for teaching that a brief and intense period of graft vs host disease is desirable as it is correlated with a clinical beneficial graft vs myeloma

effect. The Office Action asserts that Ballester teaches performing stem cell transplantation followed by DLI therapy using HLA-matched donors.

Ikehara is asserted by the Office Action to teach the advantages of performing bone marrow transplantation, in particular, for overcoming the problem of graft failure and/or rejection. The Office Action asserts that Ikehara teaches that allo-BMT using unrelated donor bone marrow has resulted in an increase of GVHD and graft failure and/or rejection. The Office Action also asserts that Ikehara teaches that hematopoietic stem cells include mobilized peripheral blood stem cells and the administration of PBSC via the portal vein after total body irradiation.

Thus, the Office Action concludes that it would have been *prima facie* obvious at the time the claimed invention was made to combine the method of Roush using stem cell transplantation and DLI to induce disease remission, with the method of Ikehara to induce tolerance to the HLA-identical stem cells mobilized from the peripheral blood. The Office Action asserts that one of skill in the art would have been motivated to make such a combination based upon the teachings of Ballester which teaches the need for a brief period of GVHD in order to attain clinical benefit and the teachings of Ikehara which teaches that immuno-tolerance is attained by transplantation of hematopoietic stem cells. Also, the Office Action states that one of skill in the art would have been motivated to use mobilized peripheral blood stem cell in place of bone marrow because it is easier to obtain peripheral blood from a HLA-identical individual than bone marrow which would require a special procedures for removal from a donor.

Applicants respectfully disagree for at least the following reasons.

Applicants note that Roush, Ballester, and Ikehara teach away from the steps of the claimed invention for the following reasons.

As acknowledged by the Office Action, "Roush teaches (DLI) therapy after stem cell transplantation [emphasis added]." In contrast, the claimed method requires performing DLI before BMT or before intravenous administration of PBSCs. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness because the claim limitations are not taught or suggested by the prior art. In fact, Roush teaches away from the claimed method because Roush discloses that the "[t]iming of DLI after SCT [allogeneic stem cell transplant] seems critical in the development of GVHD…DLI given early after SCT leads to increased risk and severity of GVHD…[and] DLI given concurrent with allogeneic SCT leads to increased GVHD in mice when compared with DLI given 21 days after SCT." (See page 168, 2nd column, 1st full paragraph of Roush).

Ballester discloses that peripheral blood AST is given on days -9 and -6 before the DLI is performed. (See "Materials and Methods" section of Ballester). In contrast, the PBSCs are administered after DLI in the method of the claimed invention.

Applicants note that Roush only teaches that DLI is performed after stem cell transplantation. Ballester only teaches that DLI is performed after peripheral blood autologous stem cells transplantation. Therefore, a person skilled in the art could only achieve the procedure of performing DLI after stem cell transplantation from the combination of Roush and Ballester, at best. The procedure that can be achieved from the combination of Roush and Ballester is completely different from the presently claimed method of the present invention.

With regard to Ikehara, it appears the Office Action is using Ikehara mainly for teaching the use of hematopoietic stem cells, such as peripheral blood cells containing hematopoietic stem cells, to improve graft failure/rejection. (See column 1, lines 55-59 and column 2, lines 29-30 of Ikehara). Ikehara also discloses the administration of the hematopoietic stem cells into the portal

vein after irradiation treatment. (See column 1, lines 62-67, column 2, lines 45-48, column 3, lines 1-2 and lines 36-38). Further, Ikehara discloses that an intravenous administration of the hematopoietic stem cells may follow the administration into the portal vein. (See column 3, lines 54-56 and Test Example 1). Nevertheless, DLI is not disclosed by Ikehara, and even if the portal administration of the hematopoietic cells supplemented with T cells may somehow be construed by the Office Action as being equivalent to DLI, the administration occurs after irradiation treatment and not before, as in the claimed method.

Further, Ikehara only teaches that bone marrow cells (BMC) can be administrated via the portal vein after TBI. Ikehara teaches that an intravenous administration of peripheral blood stem cells can be performed after the above BMC administration via the portal vein. In fact, Ikehara teaches that the combination of TBI and BMI administration via the portal vein is substantially very important. Therefore, one of ordinary skill in the art would not have had a reason or motivation to eliminate the combination of TBI and BMI administration via the portal vein.

Ikehara, Roush, and Ballester, either separately or in combination neither teaches nor suggests performing TBI as claimed in the method of the present invention. Further, even if the procedure described in Ikehara, which performs BMC administration after TBI, is combined with the procedure from the combination of Roush and Ballester, TBI is only performed before stem cell transplantation and DLI. The procedure obtained from the combination of Rousch, Ballester, and Ikehara, is completely different from the presently claimed method.

Accordingly, even if Rousch, Ballester, and Ikehara were combined, one of ordinary skill in the art would not have obtained the presently claimed method. Nor would one of ordinary

skill in the art have expected or predicted the treatment effects obtained by the presently claimed method.

Thus, because each of the documents cited by the Office Action teaches away from the claimed method, it would not have been obvious for one of ordinary skill in the art to combine the documents. However, even if one of ordinary skill in the art was motivated or had a reason to combine Roush, Ballester, and Ikehara, one of ordinary skill in the art would not be able to obtain the claimed method. At most, the combination of Roush, Ballester, and Ikehara would result in a method in which irradiation treatment is given before hematopoietic stem cell administration into the portal vein and then DLI therapy.

Reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.

3. Roush, Ballester, Carella, Ikehara, and Kushida

Claims 1, 4, 6-9, 11 and 13 rejected under 35 U.S.C. §103(a) as being unpatentable over Roush in view of f Ballester, Carella, Ikehara, and Kushida *et al.* (Blood 97: 3292-3299 (2001); "Kushida").

Roush, Ballester, Carella, and Ikehara appear to be asserted by the Office Action for the reasons discussed above.

In addition, Kushida is asserted for teaching improvements to the method of Ikehara. Kushida is asserted by the Office Action to teach injection of BM cells directly into the bone rather than the portal vein and/or i.v. injection because the donor stromal cells provided to the bone marrow allow for proliferation and differentiation of donor hematopoietic stem cells and avoid the necessity of a laparoscopic procedure and an additional i.v. injection (pages 3292-3293, bridging paragraph).

Thus, the Office Action asserts that it would have been *prima facie* obvious at the time the claimed invention was made to follow the method of Roush using stem cell transplantation and DLI to induce disease remission with GVHD and then the method of Kushida to induce tolerance to the HLA-identical stem cells in the context of a donor lymphocyte infusion as taught by Carella. The Office Action states that one of skill in the art would have been motivated to make such a combination based upon the teachings of Ballester which teaches the need for a brief period of GVHD in order to attain clinical benefit and the teachings of Ikehara which teaches that immuno-tolerance to transplanted hematopoietic stem cells is attained after irradiation. The Office Action asserts that one of skill in the art would have been motivated to modify the procedure of Ikehara with a single bone marrow injection.

The deficiencies of Roush, Ballester, Carella, and Ikehara are discussed above. Carella is mainly relied on by the Office Action for the teaching that stem cell transplantation by a donor lymphocyte infusion (DLI) may be from mobilized blood stem cells. However, Carella does not cure the deficiencies of Roush, Ballester, and Ikehara, which as discussed above, teach away from the steps of the claimed invention. Also, for that matter, one of ordinary skill in the art would have no reason or motivation to combine Carella with Roush, Ballester, and Ikehara because Carella teaches away from using TBI.

The addition of Kushida does not cure these deficiencies. Although Kushida teaches that BMCs may be transplanted by IBM-BMT after irradiation, even if one of ordinary skill in the art was motivated to make the combination asserted by the Office Action for the documents cited, one of ordinary skill in the art would not obtain the claimed invention. As discussed above, Roush discloses that the "[t]iming of DLI after SCT [allogeneic stem cell transplant] seems critical in the development of GVHD". Because the Office Action's rationale appears to be

premised upon "induc[ing] disease remission with GVHD" and Ballester is cited for the purpose of pointing out the need for a brief period of GVHD in order to attain clinical benefit, the combination of Roush, Ballester, Carella, Ikehara, and Kushida would only result in a method in which irradiation treatment is given before IBM-BMT followed by DLI therapy.

In contrast, the presently claimed method requires performing DLI before irradiation treatment and infusion of lymphocytes derived from the host or a third party with identical HLA, followed by IBM-BMT, wherein the method prevents or treats the graft versus host disease induced by donor lymphocyte infusion in the patient. In this regard, Applicants note that none of the documents disclose DLI therapy before the claimed steps of the presently claimed method.

Accordingly, because none of the cited documents teach or suggest irradiation treatment after DLI, one of ordinary skill in the art would not obtain the presently claimed method from the combination of Roush, Ballester, Carella, Ikehara, and Kushida. Nor would one of ordinary skill in the art expect or predict the treatment effects obtained by the presently claimed method.

Reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.

4. Roush, Ballester, Carella, Ikehara, and Matthes-Martin

Claims 1, 3, 4, 6-9, 11 and 13 rejected under 35 U.S.C. 103(a) as being unpatentable over Roush, Ballester, Carella, Ikehara, and further in view of Matthes-Martin, for the same reasons set forth above.

The Office Action states that it would have been prima facie obvious at the time that the claimed invention was made to use TBI as pre-transplant conditioning before the first stem cell transplant and subsequent DLI. The Office Action asserts that one of skill in the art would have been motivated to do so by the teachings of Matthes-Martin which teaches a lack of TRM associated with total body irradiation as pre-transplant conditioning.

Applicants note that because the Office Action appears to have based this rejection upon the same rationale discussed above for each of the cited documents, Roush, Ballester, Carella, Ikehara, and Matthes-Martin are deficient for the same reasons presented above. Also, even though the Office Action asserts that it would have been obvious at the time that the claimed invention was made to use TBI before the first stem cell transplant and then DLI, Carella teaches against using irradiation treatment.

As discussed above, the presently claimed method of the present invention requires irradiation treatment after DLI. Neither Roush, Ballester, Carella, Ikehara, nor Matthes-Martin, separately or in combination, teach or suggest irradiation treatment after DLI, or suggest a reason why it should be performed afterwards. Also, as acknowledged by the Office Action, the combination of Roush, Ballester, Carella, and Ikehara do not specifically teach that the conditioning regimen before the initial stem cell transplantation and DLI was total body irradiation.

Thus, one of ordinary skill in the art would not have been motivated or have a reason to combine the cited documents in order to obtain the presently claimed method. However, even if one of ordinary skill in the art was motivated to make such a combination, one of ordinary skill in the art would not arrive at the presently claimed method. Furthermore, one of ordinary skill in the art would not have expected or predicted the treatment effects obtained by the presently claimed method.

Reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.

Response To Provisional Nonstatutory Double Patenting Rejection

Claims 1, 4, 6-9, 11 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 4, 5 and 10 of copending U.S. Application No. 09/531,891 in view of Roush, Carella, and Ballester.

The Office Action asserts that claim 10 of the '891 application is drawn in part to a method of inducing immunological tolerance in a patient undergoing bone marrow transplantation in which immunological tolerance is induced comprising subjecting the patient to irradiation and administering to said irradiated patient an intra-bone marrow injection comprising an effective amount of whole bone marrow cells and a pharmaceutical carrier.

The Office Action asserts that claim 5 of the '891 application specifies that the method is for use in bone marrow transplantation. The Office Action acknowledges that the claims of the '891 application 1) do not specify that the immunological tolerance is to suppress GVHD, or that a donor lymphocyte infusion is to be administered in addition to the intra-bone marrow injection, 2) do not require that the whole bone marrow cells be from the host or an HLA-identical donor, and 3) do not provide for a first irradiation treatment prior to the donor lymphocyte infusion of part A of claim 1.

Again, Roush, Carella, and Ballester appear to be asserted by the Office Action for the same reasons set forth above.

Thus, the Office Action states that it would have been *prima facie* obvious to carry out the methods of claims 3, 4, 5 and 10 of the copending '891 application according to the method of Roush to induce tolerance by means of a IBM-BMT matched with a lymphocyte infusion. The Office Action asserts that one of skill in the art would have been motivated to do because Roush and Carella teach linking stem cell transplantation followed by DLI with both graft vs

target cell and GVHR. The Office Action assert that Ballester teaches the need for an initial period of GVHD in combination with graft vs target cell disease in order to obtain a clinical benefit. The Office Action also asserts that Carella teaches that DLI is needed for conversion to full chimerism with respect to grafted donor hematopoietic stem cells.

In response, and because prosecution of the '891 application is not complete, Applicants respectfully request that the rejection be held in abeyance.

Response To Nonstatutory Obviousness-Type Double Patenting Rejection

Claim 10 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,383,481 (Ikehara) in view of Roush, Ballester, and Sherer and Shoenfeld (Bone Marrow Transplantation 22: 873-881 (1998); "Sherer").

In addition, the Office Action asserts that Sherer teaches that autoimmune disease may be cured by allo-BMT and that GVHD mimics autoimmune disease both pathogenically and clinically.

Roush, Ballester, and Ikehara appear to be asserted by the Office Action for the same reasons set forth above.

Applicants note that obvious-type double patenting rejections are only appropriate when the cited references render the claimed invention obvious. In this case, Ikehara, Roush, and Ballester do not render the claimed method obvious for the reasons discussed above. Sherer is merely a review article, and adds nothing further to cure the deficiencies of Ikehara, Roush, and Ballester.

Further, and as discussed above, the presently claimed method requires irradiation treatment after DLI. However, none of the cited documents, including Sherer and Shornfeld, teach or suggest the performance of irradiation treatment after DLI.

Therefore, there is no teaching or suggestion that irradiation treatment may be performed after DLI or reason why such treatment should be performed after DLI from any of the references. Thus, even a person skilled in the art could not construct the method of Claim 10, which essentially requires irradiation treatment after DLI. And even a person skilled in the art cannot predict whether suitable treatment effects are obtained by the method of Claim 10 of this application.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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